UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/631,106	07/31/2003	Dennis M. Brown	67716-5003US02	7746

67374 7590 11/07/2007

MORGAN, LEWIS & BOCKIUS, LLP
ONE MARKET SPEAR STREET TOWER
SAN FRANCISCO, CA 94105

EXAMINER	
ROYDS, LESLIE A	
ART UNIT	**PAPER NUMBER**
1614	

MAIL DATE	DELIVERY MODE
11/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/631,106	BROWN, DENNIS M.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-19 and 22-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-19 and 22-30* is/are rejected.

7)☒ Claim(s) *29* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 15-19 and 22-30 are presented for examination.

A request for continued examination under 37 C.F.R. 1.114, including the fee set forth in 37 C.F.R. 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. 1.114, and the fee set forth in 37 C.F.R. 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 C.F.R. 1.114. Applicant's payment and submission filed August 27, 2007 has been received and entered into the present application. Accordingly, prosecution has been reopened.

Claims 15-19 and 22-30 are pending and under examination. Claims 26-30 are newly added.

Applicant's arguments, filed August 27, 2007, have been fully considered. Rejections not reiterated from previous Office Actions are hereby withdrawn. The following rejections are either reiterated or newly applied. They constitute the complete set of rejections presently being applied to the instant application.

Objection to the Claims (New Grounds of Objection)

Claim 29 is objected to for misspelling the word ---amonafide--- as "amonaafide" at line 5.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description Requirement

(New Grounds of Rejection)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 27-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter that was not described in the

specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Present claims 27-28 are directed to methods for, respectively, increasing the chemotherapeutic effectiveness of homoharringtonine in a patient afflicted with a homoharringtonine sensitive tumor or treating a host with a homoharringtonine sensitive solid tumor via the administration of homoharringtonine in conjunction with amonafide. Present claims 29-30 are directed to methods for, respectively, increasing the chemotherapeutic effectiveness of homoharringtonine in a patient afflicted with an amonafide sensitive tumor or treating a host with an amonafide sensitive solid tumor via the administration of amonafide in conjunction with homoharringtonine.

In particular, the specification and claims as originally filed fail to provide adequate written description for the treatment of (1) patients afflicted with a homoharringtonine sensitive tumor or, specifically, a homoharringtonine sensitive solid tumor (claims 27-28), or (2) patients afflicted with an amonafide sensitive tumor or, specifically, an amonafide sensitive solid tumor (claims 29-30).

MPEP §2163 states, "The courts have described the essential question to be addressed in a description requirement issue in a variety of ways. An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test of sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179

(Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983))...Whenever the issue arises, the fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. See, e.g., *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991)."

Applicant directs the Examiner to, e.g., Table 5 and column 6, lines 40-44, of the specification and claims as filed in support of newly added claims 27-30. However, Table 5 solely presents experimental data of the claimed combination of amonafide and homoharringtonine in RIF-1 fibrosarcoma tumor and fails to present any disclosure of any other tumor (let alone a description of the genus) that would be considered a "homoharringtonine sensitive tumor", "homoharringtonine sensitive solid tumor", "amonafide sensitive tumor" or "amonafide sensitive solid tumor" as now claimed. Furthermore, the "column 6, lines 40-44" portion of the instant specification to which Applicant has referred the Examiner in support of the newly added claims is in error because the instant disclosure does not contain columns or even line numbers beyond 30. Furthermore, the U.S. Patent Application Publication of the instant application is also not arranged in such a manner and, thus, this "column 6, lines 40-44" portion of the disclosure upon which Applicant relies in support of newly added claims 27-30 is not clearly set forth so as to be sufficiently persuasive of the fact that Applicant was in possession of these newly claimed genera of homoharringtonine and/or amonafide sensitive tumors at the time of the invention.

Accordingly, the Examiner has *fully* and carefully considered both the specification and claims as originally filed, but fails to locate adequate written support for the newly added claim limitations directed to the treatment of (1) patients afflicted with a homoharringtonine sensitive tumor or, specifically, a homoharringtonine sensitive solid tumor (claims 27-28), or (2) patients afflicted with an amonafide sensitive tumor or, specifically, an amonafide sensitive solid tumor (claims 29-30).

The instant disclosure is replete with references to the treatment of "cellular proliferative diseases" in general, particularly "neoplasia" (see, e.g., p.3 of the instant specification), as well as a single example in RIF-1 murine fibrosarcoma, but fails to present any discussion or identification of what tumors or, specifically, solid tumors, out of all neoplasia would, in fact, be "homoharringtonine-sensitive" and/or "amonafide-sensitive" such that one of ordinary skill in the art at the time of the invention would have readily recognized or understood the (solid) tumors intended by such limitations. See, e.g., MPEP §2163; *In re Lukach*, 442 F.2d 967, 169 USPQ 795 (CCPA 1971) (subgenus range was not supported by generic disclosure and specific example within the subgenus range); *In re Smith*, 458 F.2d 1389, 1395, 173 USPQ 679, 683 (CCPA 1972) (a subgenus is not necessarily described by a genus encompassing it and a species upon which it reads).

Furthermore, though Applicant may be of the persuasion that the single example in RIF-1 murine fibrosarcoma showing a prolonged tumor volume quadrupling time (TVQT) when treated with amonafide alone or homoharringtonine alone is sufficient to show that (1) RIF-1 murine fibrosarcoma is a homoharringtonine sensitive (solid) tumor or an amonafide sensitive (solid) tumor and (2) this is adequate disclosure to now claim the treatment of homoharringtonine sensitive (solid) tumor or amonafide sensitive (solid) tumors, Applicant is reminded that the instant specification is completely devoid of any disclosure as to what other types of tumor or, specifically, solid tumors, aside from this fibrosarcoma type, are sensitive to either homoharringtonine and/or amonafide and, thus, would be amenable to treatment using the presently claimed methods. In consideration of the fact that there is no disclosure to this effect in the present specification, the recitation of these newly added claim limitations directed to the treatment of patients with a homoharringtonine sensitive (solid) tumor or an amonafide sensitive (solid) tumor represents a narrowing of the subject matter disclosed in the specification and claims as originally filed. Furthermore, the mere recitation of this subgenus in the absence of *any* written support in the specification and claims as originally filed also clearly fails to convey to one of ordinary skill in the art at

the time of the invention that Applicant was, in fact, in possession of these newly claimed genera.

As stated in MPEP §2163, "The subject matter of the claim need not be described literally (i.e., using the same terms of *in haec verba*) in order for the disclosure to satisfy the description requirement." However, considering the teachings provided in the specification as originally filed, Applicant has failed to provide the necessary teachings, by describing the claimed invention, in such a way as to reasonably convey to one skilled in the relevant art that Applicant had possession of the concept of the treatment of (1) patients afflicted with a homoharringtonine sensitive tumor or, specifically, a homoharringtonine sensitive solid tumor (claims 27-28), or (2) patients afflicted with an amonafide sensitive tumor or, specifically, an amonafide sensitive solid tumor (claims 29-30).

Accordingly, the claims are considered to lack sufficient written description and are properly rejected under 35 U.S.C. 112, first paragraph.

Claim Rejections - 35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-19 and 22-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of amonafide in conjunction with homoharringtonine for the treatment of fibrosarcoma, does not reasonably provide enablement for the treatment of solid tumors generally with the combination of amonafide with homoharringtonine, for the reasons already made of record at pages 3-8 of the previous Office Action dated September 25, 2006, of which said reasons are herein incorporated by reference.

Present claim 25 is properly included in the instant rejection because the composition must be effective to perform the intended function of modulating a cellular proliferative disease, which, for the

reasons already of record at pages 3-8 of the previous Office Action dated September 25, 2006 and pages 9-16 of the Office Action dated March 24, 2006, is not enabled for the full scope of cellular proliferative diseases, but rather solely for fibrosarcoma. Such reasons will not be repeated herein so as not to burden the record. Rejection of claim 25 for lacking enablement is also made under the guidance provided in MPEP §2164.01(c), which states, "When a compound or composition claim is limited by a particular use, enablement of that claim should be evaluated based on that limitation. See *In re Vaeck*, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991)."

Newly added claim 26 is also properly included in the instant rejection because the claim is directed to a method of treating a host with a cellular proliferative disease, wherein the cellular proliferative disease is a solid tumor, which for the reasons already of record at pages 3-8 of the previous Office Action dated September 25, 2006 and pages 9-16 of the Office Action dated March 24, 2006, is not enabled for the full scope of cellular proliferative diseases, but rather solely for fibrosarcoma. Such reasons will not be repeated herein so as not to burden the record.

Newly added claims 27-30 are also properly included in the instant rejection because the instant specification fails to provide any direction or guidance as to what types of (solid) tumors were either known or suspected of being homoharringtonine sensitive or amonafide sensitive such that the skilled artisan would have had to use little more than routine experimentation to determine those tumors that were amenable to the claimed treatment method. However, absent any disclosure of what types, aside from fibrosarcoma, are specifically considered sensitive to either of the claimed active agents (i.e., homoharringtonine or amonafide), any characteristics or properties of the tumor that would be indicative of a reasonable likelihood of being sensitive to either or both of these two agents, or a definition of what would be considered "sensitive" (e.g., identification of a parameter indicative of the degree of sensitivity with at least a threshold value provided as determinative of either "sensitivity" or "non-sensitivity"), the specification lacks adequate enabling direction or guidance, either in the form of evidence or scientific

reasoning, as to what types of cancers would be sensitive to homoharringtonine and/or amonafide such that a person afflicted with such tumor(s) could be effectively treated by the presently claimed method. The lack of such direction is clear evidence that the skilled artisan would have had no alternative recourse but the burden of undue experimentation to determine what types of tumors would be responsive to the claimed treatment method. Moreover, the fact that the state of the art was such at the time of the invention that it clearly recognized the unpredictability among histologically distinct tumor types such that a response seen in one specific cancer type would not be predictive of the same (or at least similar) response in any one or more different cancer types also supports the conclusion that the skilled artisan would have been skeptical to extrapolate the efficacy seen in a single tumor type (i.e., fibrosarcoma) to the larger and much more highly (and conspicuously undefined) genera of homoharringtonine sensitive tumors and/or amonafide sensitive tumors with at least a reasonable expectation of success.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that some experimentation, even if complex, is allowable under 35 U.S.C. 112, first paragraph. Applicant again relies upon the allegation that the RIF-1 fibrosarcoma model utilized in Example 2 is one that has been used for decades as an established tumor model and, thus, the skilled artisan would have viewed successful experiments with the RIF-1 model as exemplary of success in other tumor systems. Applicant further submits that, while some experimentation would be required, it "would not be undue" (Applicant's remarks, p.6). Still further, Applicant submits that identification of solid tumors that were sensitive to homoharringtonine was within the skill of the artisan as evidenced by Jiang et al. (previously cited by the Examiner) and, thus, the identification of solid tumors that are sensitive to amonafide or homoharringtonine would not have required undue experimentation.

Applicant's traversal has been fully and carefully considered in its entirety, but fails to be persuasive.

First, Applicant continues to opine that the RIF-1 fibrosarcoma cell model is a model that "has been used for decades as an established tumor model" and that "one of skill in the art would view successful experiments with the RIF-1 model system as exemplary of success in other tumor systems", but fails to provide any evidence in support of such allegations that the RIF-1 fibrosarcoma cell model alone would have been predictive of the same (or at least substantially similar) efficacy in *any* solid tumor or even any tumor (or solid tumor) with sensitivity to either homoharringtonine or amonafide. Though Applicant previously relied upon the reference to Twentyman et al. in support of the assertion that this fibrosarcoma model was an established tumor model, the Examiner herein incorporates by reference the remarks presented in the paragraph bridging pages 6-7 of the previous Office Action dated September 25, 2006 as to why Twentyman et al., in fact, fails to support the concept that RIF-1 murine fibrosarcoma is a model that is reasonably representative of the entire breadth of solid tumor(s).

Accordingly, such allegations that RIF-1 fibrosarcoma is a model representative of other tumor systems amount to nothing more than Counsel's own speculation of the predictive efficacy of this exemplified cell model as representative of the full scope of tumors instantly claimed. This, as before, is not persuasive. Please see MPEP §2145, "The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997)".

The fact remains that, given the discussion of the unpredictability in the art at the time of the instant invention, the art (1) failed to recognize the ability to effectively treat cancerous conditions due to the challenging and complex nature of neoplasia in general and (2) also failed to recognize the ability to use a single agent for the generic treatment of any cancer or neoplastic condition or solid tumor. Please see the reference to Cecil's Textbook of Medicine as discussed at pages 9-16 of the previous Office

Action dated March 24, 2006. Applicant fails to rebut this clear presumption of unpredictability and complexity in the art by providing any arguments and/or evidence, aside from Counsel's own speculation, that the instant example of amonafide in conjunction with homoharringtonine in RIF-1 fibrosarcoma cells would have been successful in treating any other solid tumor. Though Applicant alleges in the instant remarks that the skilled artisan would have believed that the results obtained in this cell model would have been understandably predictive of similar results in other tumor systems, as well as predictive of the same efficacy in any type of solid tumor, it remains that the art overwhelmingly speaks to the contrary of this conclusion by clearly teaching that such objectives as instantly claimed by Applicant have never been achieved in the art. As a result, the idea that the efficacy seen in this single cell model would correlate to clinical success of the same degree in any solid tumor is clearly unsupported by the art at the time of the invention due to the pathophysiologic, histological and etiologic variation in solid tumor types and the fact that various tumors exhibit highly variable therapeutic responses to the same type of therapy. Accordingly, Applicant's opinion that the single cell model exemplified in the instant specification would be indicative of the same efficacy in any type of solid tumor in the absence of any evidence and/or scientific reasoning in support of this extrapolation is no more than an allegation without factual support, which is not persuasive.

Moreover, though Applicant alleges that the skilled artisan was able to determine homoharringtonine sensitive tumors without requiring undue experimentation based on the information disclosed in Jiang et al., Applicant is reminded that Jiang et al. tested homoharringtonine in 10 discrete types of solid tumors, only 4 of which demonstrated sensitivity (see Table I). This is clear evidence that a positive response indicative of sensitivity to homoharringtonine is not predictable even among various solid tumor types, let alone predictable among all tumors in general (i.e., note that claims 27 and 29 are, respectively, directed to "homoharringtonine sensitive tumors" or "amonafide sensitive tumors", which are broader genera than those claimed in claims 28 and 30, which are limited to solid tumors that are

sensitive to either agent), which are pathophysiologically, etiologically and histologically distinct from one another. Furthermore, absent any direction from Applicant as to what types, aside from fibrosarcoma, would have been sensitive to either of the claimed active agents (i.e., homoharringtonine or amonafide), any characteristics or properties of the tumor that would be indicative of a reasonable likelihood of being sensitive to either or both of these two agents, or a definition of what would be considered "sensitive" (e.g., identification of a parameter indicative of the degree of sensitivity with at least a threshold value provided as determinative of either "sensitivity" or "non-sensitivity"), the specification lacks adequate enabling direction or guidance, either in the form of evidence or scientific reasoning, as to what types of cancers would be sensitive to homoharringtonine and/or amonafide such that the artisan would not have been required to execute extensive hit or miss testing amongst a huge variety of tumors in order to determine those tumors that were "sensitive" to the claimed agents and, thus, would have been amenable to treatment via the presently claimed method.

In view of the foregoing, when all of the evidence is considered, the totality of rebuttal evidence of enablement fails to outweigh the evidence in support of the instant conclusion of a lack of adequate enabling guidance presented in the instant specification.

For these reasons, the claims remain properly rejected under 35 U.S.C. 112, first paragraph, and the rejection is **maintained**.

Claim Rejections - 35 USC § 112, Second Paragraph (New Grounds of Rejection)

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 27-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

Present claims 27-28 are directed to methods for, respectively, increasing the chemotherapeutic

effectiveness of homoharringtonine in a patient afflicted with a homoharringtonine sensitive tumor or treating a host with a homoharringtonine sensitive solid tumor via the administration of homoharringtonine in conjunction with amonafide. Present claims 29-30 are directed to methods for, respectively, increasing the chemotherapeutic effectiveness of homoharringtonine in a patient afflicted with an amonafide sensitive tumor or treating a host with an amonafide sensitive solid tumor via the administration of amonafide in conjunction with homoharringtonine.

The term "sensitive" in the phrase "homoharringtonine sensitive" or "amonafide sensitive" in claims 27-30 is a relative term which renders the claim indefinite. The term "sensitive" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention because it is unclear from the claimed context what type and degree of sensitivity is intended and how it would be determined. For example, if a tumor shows a tumor volume quadrupling time of 2 days using homoharringtonine versus 8 days using 5-fluorouracil, is that considered homoharringtonine sensitive? Would the same doses of each agent be used for comparison? The claims fail to clearly, precisely or deliberately set forth the parameter that is intended to be indicative of sensitivity, how it is to be measured and what standard would be used to make such a comparison to determine the sensitivity. Absent this information, the claims clearly fail to set forth the metes and bounds of the subject matter for which Applicant is presently seeking protection.

For these reasons, the claims fail to meet the tenor and express requirements of 35 U.S.C. 112, second paragraph, and are, thus, properly rejected.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-19 and 22-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Scheithauer et al. ("Phase II Study of Amonafide in Advanced Breast Cancer", *Breast Cancer Research and Therapeutics*, 20:63-67; 1991) in view of Jiang et al. ("Comparative *In Vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells", *Investigational New Drugs*, 1:21-25; 1983), each already of record, for the reasons of record set forth at pages 8-11 of the previous Office Action dated September 25, 2006, of which said reasons are herein incorporated by reference.

Newly added claims 27-30 are properly included in the present rejection because Scheithauer et al. teaches the treatment of patients with advanced breast cancer using amonafide at a dose of 800 mg/m2 intravenously over 3 hours repeated every 4 weeks (abstract, para. bridging col.1-2 at p.64) and further teaches that, "In summary, our results suggest that amonafide is an active agent in the treatment of patients with advanced breast cancer. The drug should therefore be considered for further evaluation and incorporation in combination chemotherapy." (p.67, col.1, last para.) Though Scheithauer et al. does not teach the concomitant use of homoharringtonine with amonafide, Jiang et al. teaches that homoharringtonine demonstrated significant antitumor activity in breast cancer (Summary, p.21). In view of such teachings, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine a therapeutically effective amount of amonafide with a therapeutically effective amount of homoharringtonine for the treatment of breast cancer because both the amonafide of Scheithauer et al. and the homoharringtonine of Jiang et al. were each known in the art to have the same efficacy in the treatment of breast cancer. Motivation to make such a combination flows logically from the very fact that each was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two compounds, when combined, would have, at minimum,

additive, if not synergistic, anticancer effects and/or increased chemotherapeutic effectiveness when combined than when used individually.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Moreover, it is noted for clarity of the record that "breast cancer" as taught by Scheithauer et al. and Jiang et al. meets Applicant's claimed limitation to a "homoharringtonine sensitive tumor" (claim 27), "homoharringtonine sensitive solid tumor" (claim 28), "amonafide sensitive tumor" (claim 29) and "amonafide sensitive solid tumor" (claim 30) because it is both (1) a solid tumor and (2) sensitive to both amonafide and homoharringtonine, as evidenced by the cited references to Scheithauer and Jiang.

Response to Applicant's Arguments

Applicant traverses the instant rejection, stating that neither reference explicitly or implicitly provides any suggestion or motivation to use amonafide in conjunction with homoharringtonine because a myriad of possible agents exist that could be used in conjunction with amonafide and that there is no motivation or suggestion to select homoharringtonine from hundreds of possible anticancer agents. Applicant further submits that this clear lack of motivation fails to provide a reasonable expectation of success.

Applicant's traversal has been fully and carefully considered in its entirety, but fails to be persuasive.

First, regarding Applicant's continued allegations of a lack of motivation to combine the references, Applicant is initially reminded that an express motivation to combine is not required to be

explicitly stated in the prior art in order to construct a finding of obviousness. Please reference MPEP §2145(X), which states, "However, there is no requirement that an express, written motivation to combine must appear in the prior art references before a finding of obviousness." Furthermore, note that the references applied under 35 U.S.C. 103(a) are not required to contain specific statements that would spell out the claimed invention in order to construct a finding of obviousness, since questions of obviousness involve not only what references expressly teach, but also what they would collectively suggest to one skilled in the art. Please reference *In re Burckel,* 201 USPQ 67 (CCPA). This was reiterated in *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007), which again forecloses the argument that a ***specific*** teaching, suggestion or motivation is required to be located in the cited art in order to support a finding of obviousness. See, e.g., *KSR International Co. v. Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007) at 1396.

Applicant's argument that there is no implicit motivation to combine amonafide with homoharringtonine because the myriad of possible agents that could be used in conjunction with amonafide is sufficiently great that, absent any motivation or suggestion to specifically pick homoharringtonine, there is no reasonable expectation of success, is not persuasive. The implicit motivation to combine amonafide with homoharringtonine results directly from the fact that each of amonafide and homoharringtonine were recognized in the art to have significant antitumor activity in breast cancer and also that Scheithauer et al. does, in fact, provide an *explicit* suggestion to use amonafide in combination chemotherapeutic regimens for the treatment of breast cancer. The very fact that each was known in the art to have the same therapeutic utility raises the reasonable expectation of success that the two agents, when combined or used in conjunction, either in a method of treating breast cancer, or in a composition for use in treating breast cancer, would have, at minimum, additive, if not synergistic, anticancer effects and/or increased chemotherapeutic effectiveness when combined than when used individually.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960). As this court explained in Crockett, the idea of combining them flows logically from their having been individually taught in the prior art. **The fact that a first component is in no way related to the second component, but where each has the same utility, does not detract from the obviousness of combining them.** *In re Linder*, 457 F.2d 506, 507 (CCPA 1972). (Holding that it would have been obvious to combine two known dispersants, since one skilled in the art would have expected a mixture of such dispersants to also be a dispersant). Moreover, picking and choosing known components from several references, each which itself discloses a plurality of such components, is permissible where each component has the same individual utility. *In re Dial*, 326 F.2d 430 (CCPA 1964). (Holding that it would have been obvious to have combined four individual stabilizers for halogenated hydrocarbon solutions from three different references, where there was no evidence in the record establishing that Applicant's claimed combination of stabilizers was any more effective or in any way otherwise different in inhibiting the decomposition of halogenated hydrocarbons than any single member of that combination. Id at 432.)"

In light of such reasoning, it remains that the use of amonafide in conjunction with homoharringtonine for use in a method of treating a solid tumor, i.e., breast cancer, or for use in a composition, would have been *prima facie* obvious to one of ordinary skill in the art, absent any factual evidence to the contrary, and further in the absence of any showing of unexpected activity or other secondary considerations (MPEP §2141).

For these reasons, and those previously made of record at pages 8-11 of the previous Office Action dated September 25, 2006, rejection of claims 15-19 and 22-30 remains proper and is **maintained**.

Double Patenting (New Grounds of Rejection)

Obviousness-Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 15-19, 22-24 and 26-30 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 50-52 and 58-59 of U.S. Patent Application No. 10/976,961 in view of Scheithauer et al. ("Phase II Study of Amonafide in Advanced Breast Cancer", *Breast Cancer Research and Therapeutics*, 20:63-67; 1991) and Jiang et al. ("Comparative *In Vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells", *Investigational New Drugs*, 1:21-25; 1983).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending application are not considered patentably distinct from each other because the pending claims are obvious over the copending claims.

The copending claims clearly provide for a method for treating cancer, such as, e.g., breast cancer, in a subject with cancer comprising the administration of an effective amount of a compound

represented by formula (I) (see copending claim 50), which provides for the use of amonafide (i.e., wherein R1 is –(CH2)nNR3R4, wherein n=2, R3 and R4 are both C1 alkyl, R2 is –NR6R7 and R6 and R7 are each also hydrogen).

Though the copending claims do not teach the concomitant use of homoharringtonine in the claimed method of administering amonafide for cancer (e.g., breast cancer), Jiang et al. teaches that homoharringtonine demonstrated significant antitumor activity in breast cancer (Summary, p.21). In view of this teaching, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine a therapeutically effective amount of amonafide with a therapeutically effective amount of homoharringtonine for the treatment of breast cancer because both the amonafide of the copending claims and the homoharringtonine of Jiang et al. were each known in the art to have the same efficacy in the treatment of breast cancer. Motivation to make such a combination flows logically from the very fact that each was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two compounds, when combined, would have, at minimum, additive, if not synergistic, anticancer effects and/or increased chemotherapeutic effectiveness when combined than when used individually.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Moreover, it is noted for clarity of the record that "breast cancer" as recited in the copending claims meets Applicant's claimed limitation to a "homoharringtonine sensitive tumor" (claim 27), "homoharringtonine sensitive solid tumor" (claim 28), "amonafide sensitive tumor" (claim 29) and "amonafide sensitive solid tumor" (claim 30) because it is both (1) a solid tumor and (2) sensitive to both

amonafide and homoharringtonine, as evidenced by the cited references to Scheithauer and Jiang.

Furthermore, it is noted that the antitumor activity of each of amonafide or homoharringtonine would have necessarily had an effect on reducing or inhibiting the growth of the tumor such that a positive response to the therapeutic regimen would have been observed as recited in the instant claims. Such a slower rate of tumor growth would have also necessarily resulted in an increase in tumor volume quadrupling time. Thus, while Applicant recites limitations wherein the modulation of the proliferative disease comprises both a reduction or inhibition of tumor growth as well as an increase in the tumor volume quadrupling time, such results are effects that would have been reasonably expected by the skilled artisan and, therefore, are not considered a patentable distinction over the copending claims.

Lastly, though the copending claims fail to recite a regimen of administration (i.e., amonafide administered before, during or after homoharringtonine; instant claims 16-18), the determination of the optimum regimen to treat a solid tumor (e.g., breast cancer) with the presently claimed active agents would have been a matter well within the purview of one of ordinary skill in the art and would have been made in accordance with a variety of factors, including, but not limited to, the dosage amount(s) to be administered based on the age, weight, sex, diet and medical condition of the patient, severity of the disease, the route of administration, pharmacological considerations, such as the activity, efficacy, pharmacokinetics and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and adverse reactions and patient tolerability to the regimen. Thus, the order of administration that would have actually been employed would have varied in accordance with these factors and, in the absence of evidence to the contrary, is not seen to be inconsistent with the order of administration that would have been readily and easily determined from the copending claims by the skilled artisan using routine experimentation.

Accordingly, rejection of claims 15-19, 22-24 and 36-30 is proper over claims 50-52 and 58-59 of U.S. Patent Application No. 10/976,961 as claiming obvious and unpatentable variants thereof.

Claim 25 is rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-44 of U.S. Patent Application No. 10/976,961 in view of Scheithauer et al. ("Phase II Study of Amonafide in Advanced Breast Cancer", *Breast Cancer Research and Therapeutics*, 20:63-67; 1991) and Jiang et al. ("Comparative *In Vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells", *Investigational New Drugs*, 1:21-25; 1983).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending application are not considered patentably distinct from each other because the pending claims are obvious over the copending claims.

The copending claims clearly provide for a pharmaceutical composition comprising an effective amount of a compound represented by formula (I) (see copending claim 42), which provides for the use of amonafide (i.e., wherein R1 is –(CH2)nNR3R4, wherein n=2, R3 and R4 are both C1 alkyl, R2 is –NR6R7 and R6 and R7 are each also hydrogen).

Though the copending claims do not teach the concomitant use of homoharringtonine in the claimed composition, Jiang et al. teaches that homoharringtonine demonstrated significant antitumor activity in breast cancer (Summary, p.21). In view of this teaching, one of ordinary skill in the art at the time of the invention would have found it *prima facie* obvious to combine a therapeutically effective amount of amonafide with a therapeutically effective amount of homoharringtonine into a pharmaceutical composition for the treatment of breast cancer because both the amonafide of the copending claims and the homoharringtonine of Jiang et al. were each known in the art to have the same efficacy in the treatment of breast cancer. Motivation to make such a combination flows logically from the very fact that

each was known in the prior art to have the same therapeutic utility and, in turn, raises the reasonable expectation of success that the two compounds, when combined, would have, at minimum, additive, if not synergistic, anticancer effects when combined than when used individually.

As stated in *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069, at page 1072 (CCPA 1980): "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the very same purpose. *In re Susi*, 58 CCPA 1074, 1079-80, 440 F.2d 442, 445, 169 USPQ 423, 426 (1971); *In re Crockett*, 47 CCPA 1018, 1020-21, 279 F.2d 274, 276-77, 126 USPQ 186, 188 (CCPA 1960)."

Accordingly, rejection of claim 25 is proper over claims 42-44 of U.S. Patent Application No. 10/976,961 as claiming obvious and unpatentable variants thereof.

Claims 15-19 and 22-30 are rejected on the grounds of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10-16 of U.S. Patent Application No. 11/676,176 in view of Scheithauer et al. ("Phase II Study of Amonafide in Advanced Breast Cancer", *Breast Cancer Research and Therapeutics*, 20:63-67; 1991) and Jiang et al. ("Comparative *In Vitro* Antitumor Activity of Homoharringtonine and Harringtonine Against Clonogenic Human Tumor Cells", *Investigational New Drugs*, 1:21-25; 1983).

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claims are either anticipated by, or would have been obvious over, the reference claims.

Although the conflicting claims are not identical, the claims of the instant patent application and those of the copending application are not considered patentably distinct from each other because the pending claims are anticipated by the copending claims.

The copending claims clearly provide for the treatment of a host, particularly a human, with a cellular proliferative disease comprising contacting said host with a naphthalimide (i.e., defined as including amonafide; see Figure 1 and para.[0025-0026], p.6 of the instant specification) in conjunction with an antiproliferative agent (i.e., defined as including homoharringtonine; see para.[0031], p.7), each in an amount sufficient to modulate said cellular proliferative disease, and further wherein the cellular proliferative disease is a solid tumor (i.e., defined as including breast cancer; see para.[015], p.3-4). The copending claims further specify that the naphthalimide is administered before, during or after the antiproliferative agent and the modulation of the disease with the combined therapy is greater than that for said antiproliferative agent alone.

For the record, it is noted that reliance upon the copending specification is permissible in accordance with the MPEP §804, which states, "The specification can be used as a dictionary to learn the meaning of a term in the patent claim. *Toro Co. v. White Consol. Indus., Inc.*, 199 F.3d 1295, 1299, 53 USPQ2d 1065, 1067 (Fed. Cir. 1999). In the instant case, the copending specification is properly relied upon in accordance with MPEP §804 to define the meaning of the terms "naphthalimide", "antiproliferative agent" and "cellular proliferative disease".

Moreover, it is noted for clarity of the record that "breast cancer" as recited in the copending claims meets Applicant's instantly claimed limitation to a "homoharringtonine sensitive tumor" (claim 27), "homoharringtonine sensitive solid tumor" (claim 28), "amonafide sensitive tumor" (claim 29) and "amonafide sensitive solid tumor" (claim 30) because it is both (1) a solid tumor and (2) sensitive to both amonafide and homoharringtonine, as evidenced by the cited references to Scheithauer and Jiang.

Furthermore, though the instant claims further recite limitations directed to the fact that the anticancer effect on the cellular proliferative disease is greater than that seen using amonafide (i.e., the "naphthalimide" of the copending claims) or homoharringtonine (i.e., the "antiproliferative agent" of the copending claims), it is noted that the very combination of two agents known individually to be effective

for the treatment of, e.g., breast cancer (see Scheithauer et al. and Jiang et al.) would have been reasonably expected to result in at least additive anticancer effects when combined than when administered individually by virtue of the fact that the shared anticancer efficacy would be increased when using a dual therapeutic combination than monotherapy alone.

Lastly, since the copending claims clearly provide for the same combination of agents as instantly claimed (i.e., amonafide in conjunction with homoharringtonine) for the treatment of the same condition (i.e., a solid tumor) as claimed, whatever effects that claimed combination of agents has in producing (1) a chemopotentiating effect (instant claim 22), (2) a cytostatic effect on increase in tumor volume quadrupling time (instant claim 23) or (3) an increase in tumor volume quadrupling time (instant clam 24) must necessarily be present in the method of the copending claims (though not explicitly recited) because products of identical composition cannot exert mutually exclusive characteristics when administered under identical circumstances or, in the instant case, identical hosts. Please see MPEP §2112.

Accordingly, rejection of claims 15-19 and 22-30 is proper over claims 1, 10-16 of U.S. Patent Application No. 11/676,176 as claiming obvious and unpatentable variants thereof.

Conclusion

Rejection of claims 15-19 and 22-30 remains proper and is **maintained**.

No claims of the present application are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (9:00 AM-5:30 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on (571)-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Leslie A. Royds
Patent Examiner
Art Unit 1614

November 2, 2007

11/4/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER